General

Guideline Title

Organ-specific management and supportive care in chronic graft-versus-host disease.

Bibliographic Source(s)

Dignan FL, Scarisbrick JJ, Cornish J, Clark A, Amrolia P, Jackson G, Mahendra P, Taylor PC, Shah P, Lightman S, Fortune F, Kibbler C, Andreyev J, Albanese A, Hadzic N, Potter MN, Shaw BE, on behalf of the Haemato-oncology Task Force of the British Committee [trunc]. Organ-specific management and supportive care in chronic graft-versus-host disease. Br J Haematol. 2012 Jul;158(1):62-78. [121 references] PubMed

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- January 4, 2016 – Noxafil (posaconazole) : The U.S. Food and Drug Administration (FDA) is cautioning that differences in dosing regimens between the two oral formulations of the antifungal Noxafil (posaconazole) have resulted in dosing errors. To help prevent additional medication errors, the drug labels were revised to indicate that the two oral formulations cannot be directly substituted for each other but require a change in dose. Direct mg for mg substitution of the two formulations can result in drug levels that are lower or higher than needed to effectively treat certain fungal infections.

Recommendations

Major Recommendations

Note from the British Committee for Standards in Haematology (BCSH): The BCSH guidelines on graft-versus-host disease have been split into three documents, which are designed to be used together and to complement each other in order to provide an evidence-based approach to managing this complex disorder. In addition to the current document, the following National Guideline Clearinghouse (NGC) summaries are available:

- Diagnosis and management of acute graft-versus-host disease
- Diagnosis and management of chronic graft-versus-host disease

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Principles of Graft-versus-Host Disease (GvHD) Management

- Patients with chronic graft-versus-host disease (GvHD) should be reviewed by a team experienced in managing transplant-related complications (1C).
- Transplant centres should establish a clinical network of specialists with an interest in GvHD to allow for multidisciplinary management (1C).
- Assessment of quality of life is recommended in all patients with GvHD (1C).
- Systemic treatment is the mainstay of therapy in patients with moderate or severe GvHD (1A).

Cutaneous GvHD

- Referral to a dermatologist with experience in transplant dermatology should be considered in patients with moderate or severe cutaneous GvHD (1C).
- All patients with GvHD on prolonged immunosuppression should have an annual skin check by a dermatologist in view of the increased risk of cutaneous malignancy (1C).
- All growing/non-healing skin lesions should be referred within 2 weeks to a dermatologist (1C).
- Emollients should be used for symptom control in skin GvHD (1C).
- Topical therapy, including steroids or topical calcineurin inhibitors, is recommended as first line therapy (1B).
- Extracorporeal photopheresis (ECP) is recommended as a second line systemic therapy for steroid-refractory skin GvHD (1B).
- Physiotherapy is recommended in patients with sclerodermoid disease (1C).

Gastrointestinal GvHD

- Referral to a gastroenterologist should be considered in patients with suspected gastrointestinal GvHD (1C).
- In view of the wide differential diagnosis, patients with diarrhoea without associated jaundice or rash suggestive of GvHD should be investigated by both upper (with duodenal aspirate and biopsies) and lower (flexible sigmoidoscopy and biopsy) gastrointestinal endoscopy in preference to colonoscopy alone (1C).
- All patients should be assessed and reviewed by a dietician with experience of managing patients with gut GvHD and each unit should have an agreed protocol for nutritional issues (1C).

Genital GvHD

- All patients should be actively questioned about genital tract symptoms (1C).
- Referral for specialist advice should be considered in all patients with difficult-to-manage genital symptoms (1C).
- High potency topical steroids (+/- topical calcineurin inhibitors) are recommended as first line therapy (1C).

Liver GvHD

- Referral for specialist hepatology opinion should be considered in patients with significant liver GvHD (1C).

Ocular GvHD

- Patients with symptoms suggestive of significant ocular involvement should be reviewed by an ophthalmologist preferably with an interest in ocular GvHD (1C).
- Patients on prolonged systemic steroids for GvHD should be aware that their vision may be reduced if they develop cataracts and should seek ophthalmic advice if this occurs (2C).
- Supportive care with artificial tears and topical anti-inflammatory/antibiotic treatment may be helpful as first line treatment (2C).

Oral GvHD

- Referral to Oral Medicine should be considered in patients with significant oral symptoms (1C).
- Topical therapies including steroid mouthwashes are recommended as first line treatment (2C).
- ECP is recommended as a second line systemic therapy for steroid-refractory GvHD (1B).

Pulmonary GvHD

- Referral to a respiratory physician should be considered in all patients with suspected pulmonary GvHD (1C).
- All patients with GvHD should be screened using pulmonary function tests regardless of symptoms (1A).
- Systemic steroids are recommended in patients with pulmonary GvHD at a dose of 1 mg/kg of prednisolone and, for those not responding, consider pulsed steroids or imatinib (2C).
- Supportive care including intravenous immunoglobulin, vaccinations, and azithromycin is also recommended (2C).

Antimicrobial Prophylaxis for Infections in GvHD

- Prophylaxis against viral, fungal, *Pneumocystis jiroveci* and *Streptococcus pneumoniae* infection should be considered in all patients receiving immunosuppressive agents for chronic GvHD (1A).
- The prophylactic and/or pre-emptive strategy for prevention of cytomegalovirus (CMV) infection including regular monitoring of CMV polymerase chain reaction adopted for haematopoietic stem cell transplantation (HSCT) recipients should be continued throughout the period of acute and/or chronic GvHD (1B).
- A mould-active azole is recommended for prophylaxis in patients undergoing treatment for GvHD (1A); suitable agents include posaconazole and voriconazole (1A) or itraconazole with regular monitoring of levels (2B).

Vaccination

- Live vaccines must not be administered in patients with GvHD (1A).
- All patients with GvHD should receive vaccination against pneumococcus, influenza, and *Haemophilus influenzae* (1B).

Complications Associated with Long-Term Steroid Use

- All patients on long-term steroid treatment should have blood pressure and glucose monitored at clinic visits and should receive gastric protection (1A).

Definitions:

Quality of Evidence

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

The original guideline document contains clinical algorithms for:

- A management approach to unexplained nausea, retching, vomiting, or anorexia
- Management of genital graft-versus-host disease (GvHD)
- Management of ocular GvHD

- Management of oral GvHD

Scope

Disease/Condition(s)

Chronic graft-versus-host disease (GvHD)

Guideline Category

Counseling

Evaluation

Management

Prevention

Treatment

Clinical Specialty

Allergy and Immunology

Dentistry

Dermatology

Endocrinology

Family Practice

Gastroenterology

Hematology

Infectious Diseases

Internal Medicine

Nutrition

Obstetrics and Gynecology

Oncology

Ophthalmology

Pediatrics

Physical Medicine and Rehabilitation

Pulmonary Medicine

Urology

Intended Users

Dentists

Dietitians

Occupational Therapists

Pharmacists

Physical Therapists

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Respiratory Care Practitioners

Guideline Objective(s)

To provide recommendations for the specific therapy of skin, oral, liver, gut, lung, ocular, and genital manifestations of chronic graft-versus-host disease (GvHD) and for the supportive care of these patients, including vaccinations and prophylaxis against infection

Target Population

Adults and children in the United Kingdom with chronic graft-versus-host disease (GvHD) following allogeneic stem cell transplant

Interventions and Practices Considered

Evaluation/Treatment/Management

General Practices

1. Patient review by an experienced team
2. Creation of an established clinical network of specialists at transplant centres
3. Assessment of patient quality of life
4. Systemic treatment for patients with moderate to severe graft-versus-host disease (GvHD)
5. Blood pressure and glucose monitoring and gastric protection with long-term steroid treatment

Cutaneous GvHD

1. Referral to a dermatologist with GvHD experience
2. Annual skin exam by a dermatologist
3. Timing of referral
4. Emollients for symptom control
5. Topical therapy (e.g., steroids, calcineurin inhibitors) as first line therapy
6. Extracorporeal photopheresis (ECP) for second line therapy in steroid-refractory GvHD
7. Physiotherapy for patients with sclerodermoid disease

Gastrointestinal GvHD

1. Referral to a gastroenterologist
2. Upper endoscopy with duodenal aspirate and biopsies and lower endoscopy (flexible sigmoidoscopy) with biopsies for diarrhoea without jaundice or rash suggestive of GvHD
3. Assessment and review by a dietician with gut GvHD experience
4. Established protocol for nutritional issues

Genital GvHD

1. Questioning patients for symptoms
2. Referral to a specialist for difficult to manage symptoms
3. High potency topical steroids with or without topical calcineurin inhibitors as first line therapy

Liver GvHD

1. Referral to a hepatologist

Ocular GvHD

1. Review by an ophthalmologist
2. Counseling patients to seek ophthalmologic assessment if cataracts develop during prolonged systemic steroid use
3. Artificial tears and topical anti-inflammatory/antibiotic treatment as first line therapy

Oral GvHD

1. Referral to Oral Medicine
2. Topical therapies including steroid mouthwashes
3. ECP as a second line systemic therapy for steroid-refractory GvHD

Pulmonary GvHD

1. Referral to a respiratory specialist
2. Screening of all GvHD patients with pulmonary function tests
3. Systemic steroids
4. Pulsed steroids or imatinib for those who do not respond to systemic steroids
5. Supportive care (e.g., intravenous immunoglobulin, vaccinations, azithromycin)

Infection Prevention

1. Regular monitoring by polymerase chain reaction for cytomegalovirus infection throughout acute and chronic GvHD
2. Prophylaxis against viral, fungal, *Pneumocystis jiroveci* and *Streptococcus pneumoniae* infection for patients receiving immunosuppressive agents
3. Treatment with a mould-active azole (e.g., posaconazole, voriconazole, or itraconazole with regular monitoring of levels)
4. Avoidance of live vaccines
5. Vaccination against pneumococcus, influenza and *Haemophilus influenzae*

Major Outcomes Considered

- Quality of life
- Incidence of developing organ-specific graft-versus-host disease (GvHD)
- Sensitivity of diagnostic tests
- Complete and partial responses to treatment
- Side effects of treatments and procedures
- Incidence of infection

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved literature review to 17th June 2011 including Medline, internet searches, and major conference reports.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The production of these guidelines involved the following step:

- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature as used to evaluate levels of evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The production of these guidelines involved the following steps:

- Establishment of a working group comprising experts in the field of allogeneic transplantation and specialists in managing graft versus host

disease (GvHD) from the following specialities: dermatology, oral medicine, hepatology, gastroenterology, ophthalmology, respiratory, endocrinology, microbiology.
- Literature review to 17th June 2011 including Medline, internet searches, and major conference reports.
- Development of key recommendations based on randomized, controlled trial evidence. Due to the paucity of randomized studies some recommendations are based on literature review and a consensus of expert opinion.
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to assess the strength of recommendations. The GRADE criteria are specified in the British Committee for Standards in Haematology (BCSH) guideline pack and the GRADE working group website (see the 'Rating Scheme for the Strength of Recommendations' field). Further information is available from the following websites:
  - http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html
  - http://www.gradeworkinggroup.org/index.htm

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The production of these guidelines involved the following steps:

- Review by the British Committee for Standards in Haematology (BCSH) committees, British Society of Blood and Marrow Transplantation (BSBMT) executive committee, the UK Photopheresis Society and the UK Paediatric Bone Marrow Transplant Group
- Review by sounding board of the British Society for Haematology (BSH) and allogeneic transplant centres in the UK

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate organ-specific management and supportive care in chronic graft-versus-host disease (GvHD), which may lead to effective control of GvHD while minimizing the risk of toxicity and relapse

Potential Harms

- Whilst there is no risk from skin atrophy with use of topical calcineurin inhibitors (tacrolimus and pimecrolimus) for cutaneous graft-versus-host disease (GvHD), patients may report a burning sensation on application and there is an increased risk of cutaneous infection. There is a potential increased risk of skin malignancies and exposure to ultraviolet (UV) light during therapy should be minimized.
- Phototherapy may be of benefit although the increased risk of skin malignancies in this group is significant, as these patients have typically received chemotherapy prior to bone marrow transplantation and subsequently immunosuppression with ciclosporin.
- Endoscopic intervention in immunosuppressed and thrombocytopenic patients is a high risk procedure.
- Intravenous ganciclovir reduces the risk of CMV disease but has no survival advantage over placebo, because of secondary neutropenia and associated infection.
- Cidofovir prevents disease but is associated with renal toxicity.

Contraindications

Contraindications

The administration of live vaccines is contraindicated in chronic graft-versus-host disease (GvHD) patients.

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology, the British Society of Blood and Marrow Transplantation nor the publishers accept any legal responsibility for the content of these guidelines.
- A discussion of all possible late effects of allogeneic transplantation is beyond the scope of this document and this guideline focuses on specific management of patients with chronic graft-versus-host disease.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Dignan FL, Scarisbrick JJ, Cornish J, Clark A, Amrolia P, Jackson G, Mahendra P, Taylor PC, Shah P, Lightman S, Fortune F, Kibbler C, Andreyev J, Albanese A, Hadzic N, Potter MN, Shaw BE, on behalf of the Haemato-oncology Task Force of the British Committee [trunc]. Organ-specific management and supportive care in chronic graft-versus-host disease. Br J Haematol. 2012 Jul;158(1):62-78. [121 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jul

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

British Society of Blood and Marrow Transplantation - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Joint Working Group of the British Committee for Standards in Haematology (BCSH) and the British Society of Blood and Marrow Transplantation (BSBMT)

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 30, 2012. The information was verified by the guideline developer on September 5, 2012. This summary was updated by ECRI Institute on January 6, 2016 following the U.S. Food and Drug Administration advisory on Noxafil (posaconazole).

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